Fingolimod (Gilenya®)
Drug Review

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Executive Summary

Introduction: Fingolimod (Gilenya®) is an oral disease-modifying agent indicated in the treatment of relapsing forms of multiple sclerosis (MS). Other disease-modifying agents indicated in the treatment of MS include: glatiramer (Copaxone®), interferon beta-1a (Avonex®, Rebif®), interferon beta-1b (Betaseron®, Extavia®), mitoxantrone (Novantrone®), natalizumab (Tysabri®), and teriflunomide (Aubagio®). Treatment guidelines for MS recommend a biologic or interferon agent as first-line therapy, but do not recommend one agent over another. Fingolimod may also be an effective first-line treatment option. Fingolimod is a sphingosine 1-phosphate receptor modulator, dose once daily, which is thought to reduce CNS inflammation in patients with MS.

Clinical Efficacy: Clinical data evaluating the efficacy of fingolimod in the treatment of MS are limited. In comparative clinical trials, relapse rate is significantly improved with fingolimod compared to either interferon beta or placebo. No clinical benefit was demonstrated with fingolimod at doses greater than 0.5 mg. Data from follow-up trials indicate sustained efficacy and no increases in adverse events for 36 months. Limited data from a subgroup analysis indicate efficacy of fingolimod treatment across patients with a wide range of clinical features.

Special Populations: Fingolimod was not studied in pregnant or lactating women, children, or adults over 65 years of age. One clinical trial evaluating fingolimod use in Japanese patients confirmed efficacy of fingolimod in this patient population.

Adverse Drug Reactions: Fingolimod has relatively good tolerability. The most common adverse events reported with fingolimod therapy include headache, elevated liver enzymes, and diarrhea. Serious adverse events associated with fingolimod therapy include cardiovascular abnormalities (bradycardia and atrioventricular (AV) block). Fingolimod therapy is associated with first-dose bradycardia occurring within 6 hours of the first dose and is only available through specialty pharmacies or the manufacturers First Dose Program. Fingolimod is metabolized by the CYP4F2 isoenzyme and has not demonstrated induction or inhibition of any of the major CYP P450 enzymes or interactions with any of the major P-glycoproteins or other transporters.

Summary: Fingolimod was the first oral disease-modifying agent approved for the treatment of relapsing multiple sclerosis. Limited comparative clinical evidence suggests fingolimod is more effective than placebo and has similar efficacy as interferon beta. Fingolimod has numerous adverse effects but they are usually only mild to moderate. Fingolimod is only available through specialty pharmacies or the manufacturers First Dose Program.

Introduction

Fingolimod (Gilenya®) is an oral disease-modifying agent indicated in the treatment of relapsing forms of multiple sclerosis (MS).[1] Fingolimod was approved by the FDA in September 2010 and was the first oral disease-modifying medication approved for treatment of multiple sclerosis.[1] An additional oral agent was recently approved for the treatment of multiple sclerosis: teriflunomide (Aubagio®).[2] Many injectable disease modifying agents are available for the treatment of MS including glatiramer (Copaxone®), interferon beta-1a (Avonex®, Rebif®), interferon beta-1b (Betaseron®, Extavia®), mitoxantrone (Novantrone®), and natalizumab (Tysabri®).[3, 4] Table 1 compares the available disease-modifying agents. This review will focus on the safety and efficacy of fingolimod in the treatment of relapsing forms of multiple sclerosis.

Disease Overview

Demyelinating diseases are neurological disorders defined by the destruction of central nervous system (CNS) tissue and are typically immune-mediated conditions.[3, 4] Multiple sclerosis (MS) is the most common demyelinating disorder and is characterized by inflammation, demyelination, scarring, and neuronal loss.[3, 4] Patients with MS can exhibit benign illness to a debilitating disease resulting in significant changes to one's lifestyle.[3, 4] Multiple sclerosis affects nearly 400,000 individuals in the United States and 2.5 million individuals worldwide.[5-7] The average estimated lifetime cost of illness from MS is estimated to be $1.2 million.[5-8] Prevalence is higher in women than men and the disease is usually diagnosed between the ages of 20 and 50 years.[5, 6, 8]

The cause of multiple sclerosis is not known.[3, 4] Both genetic (race and gender) and environmental factors (geographical location, exposure to the sun, birth month) are linked to the disease.[9-11] Immunology also plays a role; MS is thought to be an auto-immune disease mediated by T-cells that compromise the blood brain barrier and allow inflammatory mediators to enter and attack the CNS. Diagnosis of MS is based on clinical symptoms in combination with evidence of lesions on magnetic resonance imaging (MRI). Symptoms vary depending on the location and severity of the CNS lesions and may include sensory loss, optic neuritis, weakness, parasthesias, ataxia, tremor, fatigue, cognitive changes, and bladder dysfunction.[3, 4]

Multiple sclerosis (MS) is a chronic disease that can progress intermittently or continuously and is divided into four disease courses: relapsing-remitting multiple sclerosis (RRMS), primary-progressive multiple sclerosis (PPMS), secondary-progressive multiple sclerosis (SPMS), and progressive-relapsing multiple sclerosis (PRMS).[3, 4] Relapsing-remitting multiple sclerosis is the most common form of MS and is characterized by exacerbations of neurological dysfunction followed by remissions.[12] RRMS may eventually develop into secondary progressive multiple sclerosis which is characterized by a neurologic deterioration with or without relapses. Primary progressive multiple sclerosis occurs in 10-15% of patients with MS and is characterized by disease progression with some minor improvements and without any exacerbations.[11, 13] Progressive relapsing multiple sclerosis affects less than 5% of patients and is characterized by disease progression with acute relapses. Most medications used in the treatment of MS are indicated in the treatment of RRMS or SPMS; there are currently no medications labeled for use in PPMS.[3, 4]

Treatment of MS varies depending on the clinical subset of MS present and individual patient characteristics.[3, 4, 6, 8] In general, treatment may include disease modifying agents in combination with symptomatic treatment.[3, 4] Symptomatic treatments include glucocorticoid therapy, benzodiazepines, muscle relaxers, anticonvulsants, antidepressants, and medications used to treat urinary disorders.[3, 4] Currently, no curative medication therapies are available in the treatment of MS.[6, 8] Disease-modifying agents provide symptomatic relief and reduced disease progression.24 Many injectable disease-modifying agents are available for use in MS and two oral agents are available. Treatment guidelines for multiple sclerosis cite many of the biologic and interferon agents as effective treatment options, but do not recommend one therapy over another.[14-16] The interferon agents and glatiramer demonstrate reduced relapse rates and slowed disease progression and may be considered first-line therapy in RRMS.[16] Natalizumab and mitoxantrone may be considered in progressive patients who do not respond to or tolerate other disease-modifying therapies.[16] Evidence evaluating fingolimod, the oral sphingosine-1-phosphate (S1P) inhibitor, suggests fingolimod is safe and effective in reducing acute MS attacks and may be a more convenient treatment option for patients.[1, 6, 8]

Table 1. Comparison of Disease Modifying Agents used in the Treatment of Multiple Sclerosis[1, 17, 18]

Product	Drug class	Administration	Labeled uses	Unlabeled uses	Dosing	Generic Available
Fingolimod (Gilenya)	Sphingosine 1-Phosphate (S1P) Receptor Modulator	Oral; patient self-administered	Treatment of relapsing forms of multiple sclerosis (MS) to reduce the frequency of clinical exacerbations and delay disability progression	N/A	0.5mg once daily; doses >0.5mg/day associated with increased adverse events and no additional benefit	No
Glatiramer (Copaxone)	Biological	Subcutaneous; patient self-administered	Management of relapsing-remitting type multiple sclerosis, including patients with a first clinical episode with MRI features consistent with multiple sclerosis	N/A	20mg daily	No
Interferon beta-1a (Avenox)	Interferon	Intramuscular; patient self-administered or in physician's office	Treatment of relapsing forms of multiple sclerosis (MS); clinical isolated syndrome	Treatment of secondary progressive forms of multiple sclerosis (MS); to decrease the number and volume of active brain lesions, decrease overall disease burden, and delay onset of clinically definite MS in patients who have experienced a single demyelinating event.	30mcg weekly	No
Interferon beta-1a (Rebif)	Interferon	Subcutaneous; patient self-administered	Treatment of relapsing forms of multiple sclerosis (MS)	Treatment of secondary progressive forms of multiple sclerosis (MS); clinical isolated syndrome	22-44mcg three times weekly, with gradual dose titration	No
Interferon beta-1b (Betaseron, Extavia)	Interferon	Subcutaneous; patient self-administered	Treatment of relapsing forms of multiple sclerosis (MS); treatment of first clinical episode with MRI features consistent with MS	Treatment of secondary-progressive MS	62.5-250mcg every other day, with gradual dose titration	No
Mitoxantrone (Novantrone)	Anthracenedione antineoplastic agent	Intravenous; in clinic or hospital setting capable of administering chemotherapy	Initial treatment of acute nonlymphocytic leukemias (ANLL [includes myelogenous, promyelocytic, monocytic and erythroid leukemias]); treatment of advanced hormone-refractory prostate cancer; secondary progressive or relapsing-remitting multiple sclerosis (MS)	Treatment of Hodgkin lymphoma (refractory), non-Hodgkin lymphomas (NHL), acute lymphocytic leukemia (ALL), relapsed acute myeloid leukemia (AML), breast cancer (metastatic), pediatric acute myelogenous leukemia (AML), pediatric acute promyelocytic leukemia (APL); part of a conditioning regimen for autologous hematopoietic stem cell transplantation (HSCT), metastatic breast cancer, relapsed leukemia (adults), lymphoma, hepatocellular carcinoma,	12mg/m^2 every 3 months (maximum lifetime cumulative dose: 140 mg/m^2)	Yes
Natalizumab (Tysabri)	Monoclonal Antibody, Selective Adhesion-Molecule Inhibitor	Intravenous; in clinic or hospital setting	Monotherapy for the treatment of relapsing forms of multiple sclerosis; treatment of moderately- to severely-active Crohn's disease	Combination use with glatiramer or interferon beta for relapsing forms of multiple sclerosis	300mg every 4 weeks	No
Teriflunomide (Aubagio)	Pyrimidine Synthesis Inhibitor	Oral; patient self-administered	Treatment of relapsing forms of multiple sclerosis (MS)	N/A	7 mg or 14 mg once daily	No

Pharmacology

Fingolimod is a sphingosine 1-phosphate (S1P) receptor modulator that works by binding to S1P receptors and altering their activity in inflammatory processes.[3, 4] In multiple sclerosis, fingolimod appears to decrease lymphocyte movement into the CNS and results in reduced CNS inflammation.[3, 4] According to clinical data, lymphocyte count decreases up to 60% within 6 hours of the first dose of fingolimod and will return to normal 1-2 months after discontinuing the drug. Fingolimod therapy also results in decreased neutrophil count but does not reduce monocyte count.

Pharmacokinetics

Fingolimod is dosed once daily with or without food, is slowly absorbed over 6 hours and reaches maximum plasma concentrations by 12-16 hours.[1, 19-21] After administration, fingolimod is largely distributed into red blood cells, has a large volume of distribution (1,200 L), is highly plasma protein bound and is primarily metabolized by hepatic CYP4F2.[22] Fingolimod is renally excreted and no dosage adjustments are required for patients with renal or hepatic dysfunction.[1, 17, 18]

Methods

A literature search was conducted to identify articles addressing each key question, searching the MEDLINE database (1950 – 2012), the Cochrane Library, and reference lists of review articles. For the clinical efficacy section, only clinical trials published in English and indexed on MEDLINE 1/2011 to 2/2013, evaluating efficacy of fingolimod with reduction of symptoms or improvement in disease state as an endpoint are included. Trials evaluating fingolimod as monotherapy or combination therapy where adjunctive medications remained constant throughout the trial are included. Trials comparing monotherapy with combination regimens were excluded. The following reports were excluded (note: some were excluded for more than 1 reason):

- Individual clinical trials which evaluated endpoints other than reduction of symptoms, such as lymphocyte count[23-25], cost-effectiveness[26], quality of life[27], or immune response[28, 29].
- Individual trials comparing fingolimod in dose-finding studies or in healthy volunteers.[19-22, 30-36]
- Individual clinical trials without access to the full article.

Clinical Efficacy

Seven clinical trials are available evaluating the efficacy of fingolimod in the treatment of relapsing multiple sclerosis.[37-43] Three randomized controlled trials compared fingolimod to placebo or interferon beta,[37, 39, 40] three non-comparative

extension trials evaluated the long-term efficacy of fingolimod, and one sub-group analysis assessed relapse and disability outcomes.[38, 41] The studies evaluated patients (predominantly Caucasian, adult women) with symptoms and a magnetic resonance imaging (MRI) scan indicative of relapsing multiple sclerosis. Patients with a score of 0-6 out of 10 on the Expanded Disability Status Scale (EDSS; higher scores indicate greater disability) were included. Patients received fingolimod doses of 0.5-5 mg once daily for up to 36 months. All trials evaluated the relapse rate, defined as a new or worsening symptom and an increase in EDSS score of 0.5 or more.

Cohen et al[37] evaluated 1292 patients randomized to receive fingolimod 0.5 mg or 1.25 mg once daily or intramuscular interferon beta-1a (Avonex®) 30 mcg once weekly for 12 months. Relapse rates were significantly lower in the fingolimod treatment groups (0.16-0.2) compared to the interferon beta treatment group (0.33, $p<0.001$). The number of new or enlarged lesions on MRI was significantly higher in the interferon beta group compared to the fingolimod groups ($p<0.005$) at 12 months. No significant differences in relapse rate or number of lesions occurred between the fingolimod treatment groups. No significant difference in progression of disability occurred in any of the treatment groups. Adverse events were mild to moderate and similar across treatment groups.

Willing patients from the trial by Cohen et al[37] enrolled in a follow-up study for up to 2 years.[43] Patients in the fingolimod treatment group continued the same treatment and patients originally randomized to receive interferon beta-1a were randomly reassigned to receive fingolimod 0.5 mg or 1.25 mg once daily. Patients in the continuous fingolimod treatment group demonstrated persistent benefits in relapse rates and number of lesions over 24 months and reported lower relapse rates and number of lesions compared to patients switched from interferon to fingolimod ($p<0.05$) at 24 months. Relapse rate and the number of new or enlarged lesions on MRI were significantly improved in the interferon switched to fingolimod treatment groups at 24 months ($p<0.05$). No change in disability progression was reported in any of the treatment groups. Adverse event rates were similar across treatment groups at 12 and 24 months.

Kappos et al (2010)[40] evaluated 1,272 patients randomized to receive fingolimod 0.5 mg or 1.25 mg or placebo once daily for 24 months. A total of 1,272 patients were randomized and 1,033 patients (81.2%) completed the study with 945 patients (74.3%) still receiving fingolimod at the end of the trial. Relapse rates were significantly lower in the fingolimod treatment groups (0.16-0.18) compared to placebo (0.40, $p<0.001$). The number of new or enlarged lesions on MRI was significantly higher in the placebo group compared to the fingolimod groups ($p<0.001$) at 24 months. Adverse events were similar across treatment groups; however, adverse event discontinuation rate was higher in the fingolimod 1.25 mg treatment group (14.2%) compared to the fingolimod 0.5 mg (7.5%) or placebo (7.7%) treatment groups.

A sub-group analysis of patients enrolled in the Kappos et al (2010)[40] trial is available evaluating the efficacy of fingolimod in subgroups of patients with different baseline characteristics.[42] Subgroups included sex, age, baseline disability scores and lesion parameters, and response to previous therapy. Relapse rates were significantly

lower than placebo across all subgroups except for in patients aged over 40 years. This limited evidence suggests patients with relapsing-remitting MS with a wide spectrum of clinical and MRI features may benefit from fingolimod treatment.

Kappos et al (2006)[39] evaluated patients with both relapsing-remitting multiple sclerosis and secondary progressive multiple sclerosis randomized to receive fingolimod 1.25 mg or 5 mg or placebo for 6-12 months. The total number lesions on MRI was significantly higher in the placebo group (14.8) compared to the fingolimod groups (5.7-8.4, $p<0.001$) at 6 months. The study was not powered to find a difference in relapse rate between treatment groups. Adverse event rates were higher in the fingolimod 5 mg treatment group (96%) compared to placebo (82%, $p<0.05$). No differences in adverse event rates were reported between the fingolimod 1.25 mg treatment group and placebo. Liver enzymes were significantly elevated in the fingolimod treatment groups (10-12%) compared to placebo (1%) at 6 months.

Willing patients from the trial by Kappos et al (2006)[39] enrolled in a follow-up study for an additional 1-2 years.[38, 41] Patients originally randomized to receive fingolimod 5 mg were reassigned to receive fingolimod 1.25 mg because an increase in adverse effects with no added clinical benefit occurred with the 5 mg dose. At 24 months, improvements in number of lesions and relapse rate were sustained and similar to results at 12 months.[41] The majority of patients continued to be lesion free (88-89%) and relapse free (68-73%) for up to 36 months.[38] No significant increases in adverse event rate were reported over the 36 months.

Clinical data evaluating the efficacy of fingolimod in the treatment of MS are limited. In comparative clinical trials, relapse rate was significantly improved with fingolimod (0.16-0.31) compared to either interferon beta (0.33) or placebo (0.4) with 1-2 years of treatment. No clinical benefit was demonstrated with fingolimod at doses greater than 0.5 mg. Data from follow-up trials indicate sustained efficacy and no increases in adverse events with long-term fingolimod treatment. Limited data from a subgroup analysis indicate efficacy of fingolimod treatment across patients with a wide range of clinical features. Overall, fingolimod is an efficacious treatment option for patients with relapsing multiple sclerosis.

Special Populations

One randomized clinical trial evaluating the safety and efficacy of fingolimod treatment in 171 Japanese patients with relapsing MS is available.[44] Patients were randomized to receive fingolimod 0.5 mg or 1.25 mg daily or placebo for six months. Higher rates of lesion free MRIs were reported in the fingolimod treatment groups (70-86%) compared to placebo (40%, $p<0.05$). No differences in relapse rates were reported. Total adverse events, serious adverse events, and adverse event discontinuation rates were reported more frequently in the fingolimod treatment groups compared to placebo.

Fingolimod was not studied in pregnant or lactating women, children, or adults over 65 years of age.[1, 17, 18] No pharmacokinetic differences were reported between males and females treated with fingolimod. Animal data suggest there may be increased risk of fetal birth defects or death. No fingolimod dosage adjustment is recommended in patients with renal impairment or hepatic insufficiency.[1, 17, 18] In a trial evaluating the effects of severe hepatic impairment on fingolimod, overall exposure doubled, the half-life was increased by 50% and the authors of the trial recommend reducing the fingolimod maintenance dose by 50% in patients with severe hepatic impairment.[33]

Adverse Drug Reactions

Although fingolimod has numerous adverse effects, it has good tolerability relative to alternative MS therapeutic agents. Adverse effects associated with fingolimod are frequent but usually only mild to moderate. The most common adverse events reported with fingolimod therapy include headache (25%), elevated liver enzymes (14%), diarrhea (12%), and cough (10%).[1, 17, 18] Serious adverse events associated with fingolimod therapy include cardiovascular abnormalities (bradycardia (4%) and atrioventricular (AV) block) and patients most commonly discontinued therapy due to elevated liver enzymes (up to three times the normal value).[1, 17, 18] Fingolimod therapy is associated with first-dose bradycardia (reduction of about 10-13 beats/min) within 6 hours of the first dose and resolving within 24 hours.[1, 17, 18] Because of this, fingolimod is only available through specialty pharmacies or the manufacturers First Dose Program.[17, 18] In a 3 year clinical trial, fingolimod was generally well tolerated. Upper respiratory infection, nasopharyngitis, headache, dyspnea, fatigue, and influenza were the most frequently reported adverse events.[38] Asymptomatic liver enzyme elevation, increased blood pressure, and bradycardia and heart block occurred throughout the 36 month period.[38]

Fingolimod is metabolized by the CYP4F2 isoenzyme which primarily metabolizes endogenous substances.[1, 17, 18] Fingolimod has not demonstrated induction or inhibition of any of the major CYP P450 enzymes or interactions with any of the major P-glycoproteins or other transporters. Although drug interactions may occur, clinical studies have failed to demonstrate any significant drug-drug interactions.[22, 30] Theoretical or additive effects may occur with coadministration of fingolimod and ketoconazole, beta-blockers, and antiarrhythmic agents.[22, 30] Administration of fingolimod in combination with immunosuppressant agents may result in increased immunosuppression.[1, 17, 18]

Summary

Fingolimod is a sphingosine 1-phosphate receptor modulator indicated in the treatment of relapsing-remitting multiple sclerosis. Fingolimod is dosed once daily and was the first oral disease-modifying agent approved for use in MS. Higher than recommended doses produce increased side effects without increased benefit. The exact

mechanism of action of fingolimod is not known but it is thought to alter lymphocyte activity in inflammatory processes and reduce CNS inflammation. Treatment guidelines for multiple sclerosis recommend many of the biologic and interferon agents as effective treatment options, but do not recommend one therapy over another. Limited comparative clinical evidence is available for fingolimod and of the available disease modifying agents, comparative evidence is only available for fingolimod versus the interferon products. In the available comparative trials, fingolimod demonstrated similar efficacy as interferon beta. In placebo-controlled trials, fingolimod therapy significantly reduced disability progression at 3 and 6 months compared to placebo and the benefits of fingolimod therapy were demonstrated for up to 36 months. Fingolimod has numerous adverse effects but they are usually only mild to moderate. The most common adverse events reported with fingolimod therapy include headache, elevated liver enzymes, and diarrhea. The most serious adverse events associated with fingolimod therapy are cardiovascular abnormalities and first-dose bradycardia. Fingolimod is only available through specialty pharmacies or the manufacturers First Dose Program.

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